AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Gefitinib (IRESSA™, ZD1839)
Study Code	D791AC00007
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An Open Label, Randomised, Parallel Group, Multicentre, Phase III Study to Assess Efficacy, Safety and Tolerability of Gefitinib (IRESSA™) (250mg tablet) Versus Carboplatin / Paclitaxel Doublet Chemotherapy as First-Line Treatment in Selected Patients with Advanced (Stage IIIB or IV) Non-Small Cell Lung Cancer (NSCLC) in Asia (IPASS)

Study dates:	First patient enrolled: 29 March 2006 Data cut-off date: 14 April 2008
Phase of development:	Therapeutic confirmatory (III)
International Co-ordinating Investigator:	
Sponsor's Responsible Medical Officer:	Dr Alison Armour MB ChB, BSc, MSc, MD, MRCP, FRCR Medical Science Director – IRESSA, AstraZeneca, Alderley Park, Macclesfield, Cheshire, SK10 4TG, UK

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents

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Study centres

A total of 87 centres from the following countries participated in the study: China, Hong Kong, Indonesia, Japan, Malaysia, Philippines, Singapore, Taiwan, and Thailand.

Publications

Mok T, Wu Y-L, Thongprasert S, Yang C-H, Chu D, Saijo N, et al. Phase III, randomised, open-label, first-line study of gefitinib vs carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer (IPASS). Ann Oncol 2008; 19 (Suppl 8): viii1, abs LBA2, DOI:10.1093/annonc/mdn649.

Objectives

The primary objective of this study was to compare gefitinib with carboplatin / paclitaxel doublet chemotherapy given as first-line treatment in terms of progression free survival (PFS) in selected non-small cell lung cancer (NSCLC) patients (non-inferiority).

The secondary objectives of the study were:

- to compare the randomized treatment arms in terms of overall survival (OS),

and to compare gefitinib with carboplatin / paclitaxel doublet chemotherapy given as first-line treatment in terms of:

- objective tumour response rate according to Response Evaluation Criteria in Solid Tumours (RECIST)
- the safety and tolerability profile of gefitinib at a 250 mg daily dose relative to that of carboplatin / paclitaxel doublet chemotherapy.
- quality of life (QOL) as measured by the total score and Trial Outcome Index (TOI) of the Functional Assessment of Cancer Therapy – Lung Cancer (FACT-L) questionnaire
- symptom improvement as measured by the Lung Cancer Subscale (LCS) of the FACT-L questionnaire

The exploratory objectives of the study were:

- to compare gefitinib with carboplatin / paclitaxel doublet chemotherapy given as first-line treatment in terms of health care resource use in a subset of patients.
- to investigate baseline biomarker data in consenting patients to ascertain if there are any biomarkers that differentiate for a relative treatment effect when comparing the randomised treatment arms.

Study design

This was an open label, multicentre, randomised (1:1), parallel group, Phase III study comparing gefitinib (Arm A) to carboplatin / paclitaxel doublet chemotherapy (Arm B) in patients with stage IIIB or stage IV adenocarcinoma of the lung in the first-line setting. It was the protocol intent that, in Arm A, patients progressing on gefitinib were to be treated with carboplatin / paclitaxel doublet chemotherapy. Investigators could, however, decide to treat with another approved therapy of their choice if they felt the patient was unsuitable to receive carboplatin / paclitaxel doublet chemotherapy. Following progression on carboplatin / paclitaxel doublet chemotherapy in either Arm A or B, further care and treatment was at the discretion of the treating physician.

Target patient population and sample size

The target population was male or female never smokers or light ex-smokers with stage IIIB or stage IV adenocarcinoma of the lung who had not received any previous chemotherapy (excluding non-platinum based adjuvant chemotherapy). The study was conducted in patients in Asia. Light ex-smokers were defined as those that had ceased smoking at least 15 years before Day 1 of study treatment and who had smoked 10 pack-years or fewer.

A total of 944 progression events were needed in order to rule out a HR (gefitinib: carboplatin/paclitaxel) of 1.2, ie, that median PFS on gefitinib was no more than 1 month less than the 6 months expected with carboplatin/paclitaxel. This number of events was required to give 80% chance (power) of concluding non-inferiority (if gefitinib was truly non-inferior to carboplatin/paclitaxel) with a 2-sided 5% chance (significance level) of concluding non-inferiority in error. With a recruitment period of 20 months and 1212 patients randomised (606 per treatment arm) then a follow up period of 6 months was expected be sufficient to observe the required 944 progression events.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

The gefitinib dose level for this study was 250 mg once daily. One tablet of gefitinib was taken orally at each administration, about the same time everyday, with or without food. If the patient forgot to take a dose, they were to take the last missed dose as soon as they remembered, as long as it was at least 12 hours before the next dose was due. The gefitinib formulation was F12653 and batch numbers were 2000065541, 2000065546, 2000089095, 2000095793, and 2000091243.

Patients received paclitaxel 200 mg/m^2 intravenous (iv) over 3 hours on Day 1, immediately followed by carboplatin AUC 5.0 or 6.0 IV over 15 to 60 minutes, repeated in cycles of 3 weeks for a total of 6 cycles. Batch numbers are not provided for carboplatin and paclitaxel as they are non-investigational products and were provided from commercial stock.

Duration of treatment

The investigational product, gefitinib, was to be taken daily until the patient had documented objective progressive disease (PD) or until other criteria for discontinuation were met.

Paclitaxel and carboplatin were administered on Day 1, repeated in cycles of 3 weeks for a total of 6 cycles. Chemotherapy was to be discontinued if there was objective PD or other criteria for discontinuation were met.

Patients who discontinued treatment on either arm for any reason without documented objective PD continued to attend clinic visits and tumour assessments until PD was documented.

Survival follow up began upon documentation of PD. All subsequent chemotherapy, radiation, surgical or other anti-cancer therapy, were to be recorded until death.

Criteria for evaluation - efficacy (main variables)

- Primary variable: progression free survival (PFS) using RECIST criteria

- Secondary variables: OS (early analysis, OS follow up ongoing); objective tumour response rate (ORR) as per RECIST; QOL (FACT-L and TOI) and symptom improvement (LCS of FACT-L), as measured by percentage of patients with improvement in FACT-L total, TOI, and LCS scores, time to worsening in FACT-L total, TOI, and LCS scores, and survival without CTC grade 3 or 4 toxicity (pre-planned).

Criteria for evaluation - safety (main variables)

- Secondary variables: nature, incidence and severity of adverse events (AEs) and serious adverse events (SAEs); incidence of and reasons for study drug dose interruptions and withdrawals; laboratory assessments and physical examinations.

Statistical methods

The primary outcome variable PFS was analysed in the ITT population using a proportional hazards model adjusted for WHO performance status (0, 1 vs. 2), smoking history (never vs. light ex-smoker), and gender. The HR (gefitinib: carboplatin/paclitaxel) was estimated together with its 2-sided 95% CI and p-value. The null hypothesis of PFS inferiority would be rejected, and hence non-inferiority concluded, if the upper 95% confidence limit (CL) lay below 1.2. If non-inferiority was concluded, and if the upper 95% CL for the HR lay below 1.0, then superior PFS for gefitinib would be declared (closed test procedure).

The analysis of OS is powered and sized to produce a statistically meaningful analysis at a later date, when 944 deaths have occurred. However, an early analysis of OS has been performed at the time of the primary analysis (PFS) to give an indication of effect size. The HR with 95% CI for gefitinib compared to carboplatin/paclitaxel was estimated using a proportional hazards model adjusting for randomised treatment and the same covariates as used in the analysis of PFS. It is important to note that the OS comparison in this study is essentially comparing gefitinib followed by carboplatin/paclitaxel followed by investigator choice versus carboplatin/paclitaxel followed by investigator choice.

Additionally, OS will be very difficult to interpret in this study due to the large range of subsequent treatment that patients will receive, and the fact that these treatments are likely to differ between randomised groups. In particular, it was the protocol intent that patients in the gefitinib treatment arm should receive carboplatin / paclitaxel, if appropriate, following progression with gefitinib. Therefore, PFS is the appropriate primary endpoint for the study, and little weight should be given to OS scientifically in this study.

ORR was compared between the randomised treatment groups using a logistic regression model with the same covariates as PFS. The odds ratio (OR) for treatment (gefitinib: carboplatin/paclitaxel) was estimated from the model along with its associated 95% CI and p-value.

QOL improvement rates in the FACT-L total score and TOI and symptom improvement rates as measured by the LCS subscale were analysed in the same way as ORR. Time to worsening in the FACT-L total score, TOI and the LCS subscale was summarised but not formally analysed. Survival without CTC grade 3 or 4 toxicity was analysed by estimating a HR, 95% CI and p-value for gefitinib versus carboplatin/paclitaxel from a proportional hazards model using the same covariates as the analysis of PFS.

A formal statistical comparison of first-line randomised treatments was performed for ten pre-specified safety events (AEs or laboratory changes; five possibly associated with carboplatin/paclitaxel and five possibly associated with gefitinib) using Fisher's exact test, with multiplicity adjustment using the Westfall and Young method.

One pre-planned interim analysis was conducted following 173 PFS events. The purpose of this analysis was to test for inferiority of first-line gefitinib compared to first-line carboplatin/paclitaxel in terms of PFS. No adjustment of significance level was applied for the planned final analysis of PFS as there was no opportunity to stop the study early at the interim analysis due to early achievement of non-inferiority for PFS. The interim analysis was performed independently and all AstraZeneca personnel remained blind to the results. The Independent Data Monitoring Committee recommended the study should continue as planned to completion.

Patient population

A total of 1217 patients were randomised to treatment and included in the ITT population (gefitinib: 609 and carboplatin / paclitaxel: 608). The safety population included 1196 (98.3%) patients (gefitinib: 99.7% and carboplatin / paclitaxel: 96.9%). The per-protocol population included 1177 (96.7%) patients (gefitinib: 98.0% and carboplatin / paclitaxel: 95.4%). The evaluable for QOL population included 1151 (94.6%) patients (gefitinib: 96.9% and carboplatin / paclitaxel: 92.3%).

All patients randomised to carboplatin / paclitaxel had discontinued study treatment by the time of the data cut-off. This is expected since any patients not discontinued treatment by data cut-off because of progression, AEs etc, had discontinued treatment because they had received the maximum number of 6 cycles of treatment with carboplatin / paclitaxel. In the gefitinib

group, 24.5% of patients continued to receive gefitinib at the time of data cut-off. At data cut-off, 59.4% of patients randomised to gefitinib, and 54.6% of patients randomised to carboplatin / paclitaxel were continuing in the study. The remainder of the patients had died (37% in both treatment arms), had withdrawn consent (3.1% in the gefitinib arm and 7.6% in the carboplatin / paclitaxel arm) or were lost to follow up (0.8% in the gefitinib arm and 0.3% in the carboplatin / paclitaxel arm)

Demographic and baseline characteristics were well balanced between the two treatment groups and the population was representative of the advanced NSCLC population clinically selected for this study. The majority of patients were female (79%) and the median age was 57 years. The majority (94%) of patients had never smoked. Evaluable biomarker samples were available for approximately 40% of patients. The percentage of patients with a positive status out of the total with a known status was 60% for EGFR mutation status, 61% for EGFR FISH status and 73% for EGFR protein expression status.

Summary of efficacy results

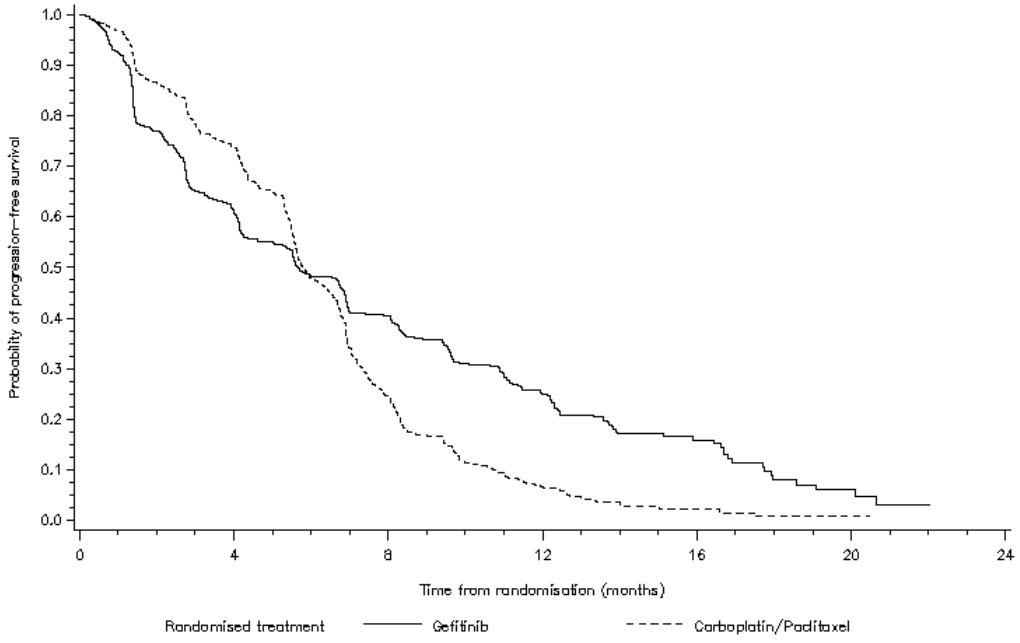
Primary efficacy results

- The study exceeded its primary objective and demonstrated superiority of gefitinib relative to carboplatin / paclitaxel in terms of PFS: HR 0.74, 95% CI 0.65 to 0.85, $p<0.0001$. The upper CL for the HR fell below the non-inferiority limit of 1.2, and below the superiority limit of 1.0.

  – The risk of progression over a given period was reduced by 26% on gefitinib compared with carboplatin / paclitaxel (this translates to a 35% prolongation in PFS over the entire study period assuming constant event rates).

  – The HR was not constant over time, with the probability of being progression free in favour of carboplatin / paclitaxel doublet chemotherapy in the first 6 months, and in favour of gefitinib in the following 16 months (see Figure S1). This was likely to be because of the different effect of gefitinib in subgroups defined by EGFR mutation status (see below).

Figure S1 Kaplan-Meier curves for the primary analysis of PFS (ITT Population)

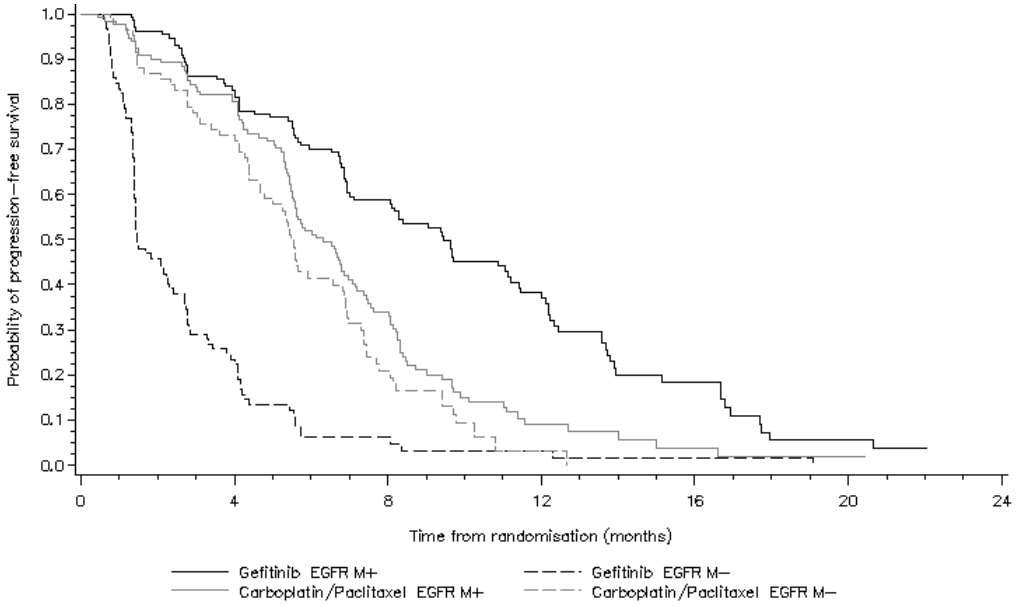


Number of patients at risk

Months	0	4	8	12	16	20	24
Gefitinib	609	363	212	76	24	5	0
Carboplatin/Paclitaxel	608	412	118	22	3	1	0

– The pre-planned analysis of the biomarker data was an exploratory objective since tissue collection was not mandatory for all patients. PFS was significantly longer for gefitinib than carboplatin / paclitaxel in EGFR mutation positive patients (HR 0.48, 95% CI 0.36 to 0.64, p<0.0001), and significantly longer for carboplatin / paclitaxel than gefitinib in patients who did not have a detectable EGFR mutation (defined as mutation negative) (HR 2.85, 95% CI 2.05 to 3.98, p<0.0001) (treatment by EGFR mutation interaction test p<0.0001). Within these subgroups, the HR appeared to be constant over time and the Kaplan-Meier curves did not cross (Figure S2). In patients with unknown mutation status, PFS results (HR 0.68, 95% CI 0.579 to 0.808, p<0.0001) were similar to that of the overall population.

Figure S2 Kaplan-Meier curves for the analysis of PFS by known mutation status (ITT Population)



Number of patients at risk:

Months	0	4	8	12	16	20	24
Gefitinib M+	132	108	71	31	11	3	0
Gefitinib M–	91	21	4	2	1	0	0
Carboplatin/Paclitaxel M+	129	103	37	7	2	1	0
Carboplatin/Paclitaxel M–	85	58	14	1	0	0	0

– A similar trend, likely to be driven by EGFR mutation status due to the overlap between FISH and mutation status, was seen in analyses by EGFR FISH status (HR 0.66, 95% CI 0.50 to 0.88, p=0.0050 in patients with FISH positive status and HR 1.24, 95% CI 0.87 to 1.76, p=0.2368 in patients with FISH negative status) (treatment by EGFR FISH interaction test p=0.0437).

Secondary efficacy results

- OS was similar for both treatments (HR 0.91, 95% CI 0.76 to 1.10; 37% of patients had died). Further survival follow-up is ongoing (note that survival is likely to be influenced by subsequent treatments).

  – A total of 237 (38.9) patients received carboplatin / paclitaxel at some point following gefitinib first-line therapy. In the carboplatin / paclitaxel group, 240 (39.5%) received EGFR TKIs at some point following first-line carboplatin / paclitaxel treatment. Therefore there was a large degree of crossover, and it was balanced between the randomised treatment arms.

  – In post-hoc analyses of OS by EGFR mutation status, OS was numerically longer for gefitinib in the EGFR mutation positive subgroup and numerically

longer for carboplatin / paclitaxel in the EGFR mutation negative subgroup. There was no statistically significant difference between these subgroups, but it is acknowledging that there were only a small number of events in this analysis. OS in the EGFR mutation unknown subgroup was similar to the overall population.

- ORR was superior for gefitinib (43.0%) compared with carboplatin / paclitaxel (32.2%) (OR 1.59, 95% CI 1.25 to 2.01, p=0.0001).

  - In pre-planned analyses of ORR by EGFR mutation status, in the EGFR mutation positive subgroup, ORR was 71.2% and 47.3% in the gefitinib and carboplatin / paclitaxel treatment arms, respectively. In the subgroup of patients who were EGFR mutation negative, ORR was 1.1% (one patient) and 23.5% in the gefitinib and carboplatin / paclitaxel treatment arms, respectively. In the EGFR mutation unknown subgroup, ORR was 43.3% and 29.2% in the gefitinib and carboplatin / paclitaxel treatment arms, respectively.

- Significantly more gefitinib-treated patients experienced a clinically important improvement in QOL compared with carboplatin / paclitaxel (48% compared with 41%, OR 1.34, 95% CI 1.06 to 1.69, p=0.0148 for FACT-L total score; 46% compared with 33%, OR 1.78, 95% CI 1.40 to 2.26, p<0.0001 for TOI).

  - In post-hoc analyses by EGFR mutation status, in the EGFR mutation positive subgroup, significantly more gefitinib-treated patients experienced a clinically important improvement in QOL compared with carboplatin / paclitaxel (70% compared with 45%, for FACT-L total score; 70% compared with 38%, for TOI). In the EGFR mutation negative subgroup, significantly fewer gefitinib-treated patients experienced a clinically important improvement in QOL compared with carboplatin / paclitaxel (15% compared with 36%, for FACT-L total score; 12% compared with 29%, for TOI). In the EGFR mutation unknown subgroup, significantly more gefitinib-treated patients experienced a clinically important improvement in QOL compared with carboplatin / paclitaxel (48% compared with 41%, for FACT-L total score; 46% compared with 32%, for TOI).

- Disease-related symptom improvement rates were similar for gefitinib and carboplatin / paclitaxel (52% compared with 49%, OR 1.13, 95% CI 0.90 to 1.42, p=0.3037).

  - In post-hoc analyses of disease-related symptom improvement by EGFR mutation status, in the EGFR mutation positive subgroup, significantly more gefitinib-treated patients experienced a clinically important improvement compared with carboplatin / paclitaxel (76% compared with 54%). In the EGFR mutation negative subgroup, significantly less gefitinib-treated patients experienced a clinically important improvement compared with carboplatin /

paclitaxel (20% compared with 48%). In the EGFR mutation unknown subgroup, disease-related symptom improvement rates were similar for gefitinib and carboplatin / paclitaxel (51% compared with 47%).

- Times to worsening in QOL (as measured by FACT-L and TOI) and disease-related symptoms (as measured by LCS) were longer in the gefitinib arm compared with the carboplatin / paclitaxel arm (medians of 8.3, 9.7 and 7.1 months, respectively with gefitinib and 2.5, 2.8 and 3.1 months , respectively with carboplatin / paclitaxel).

  – In post-hoc analyses by EGFR mutation status, in the EGFR mutation positive subgroup, times to worsening were substantially longer in the gefitinib arm compared with the carboplatin / paclitaxel arm. In the EGFR mutation negative subgroup, times to worsening were similar or shorter in the gefitinib arm compared with the carboplatin / paclitaxel arm. In the EGFR mutation unknown subgroup, times to worsening were longer in the gefitinib arm.

- Survival without CTC Grade 3/4 toxicity was significantly longer for gefitinib compared with carboplatin / paclitaxel (HR 0.34, 95% CI 0.29 to 0.38, $p<0.0001$).

Summary of safety results

Median exposure to gefitinib was 5.6 months and 4.1 months to carboplatin / paclitaxel doublet chemotherapy (mean exposure of 6.4 and 3.4 months, respectively). The median (mean) number of carboplatin / paclitaxel cycles administered was 6.0 (4.6). The majority of patients received 4 to 6 cycles of carboplatin / paclitaxel therapy: 316 (53.7%) patients received 6 cycles, 42 (7.1%) received 5 cycles, 79 (13.4%) received 4 cycles, 36 (6.1%) received 3 cycles, 69 (11.7%) received 2 cycles, and 47 (8.0%) received 1 cycle.

Gefitinib had a more favourable tolerability profile than carboplatin / paclitaxel doublet chemotherapy, indicated by fewer CTC grade 3, 4 or 5 AEs (31.6% versus 62.5%), fewer dose modifications due to toxicity (16.1% versus 35.2% [carboplatin]/37.5% [paclitaxel]) and fewer AEs leading to discontinuation of randomised treatment (6.9% versus 13.6%). The number of patients with AEs with an outcome of death was low and was similar for both treatments (23 [3.8%] patients in the gefitinib arm and 16 [2.7%] patients in the carboplatin / paclitaxel arm).

AEs more commonly reported with gefitinib were generally consistent with its prescribing information, previous gefitinib studies in the relapsed setting, and underlying disease; these included rash/acne, dry skin, paronychia, nail and nail bed conditions, diarrhoea, stomatitis, pruritus, and liver transaminase elevations. AEs more commonly reported with carboplatin / paclitaxel were generally consistent with the literature and underlying disease; these included neurotoxicity, haematological toxicity, alopecia, nausea, asthenic conditions, myalgia, arthralgia, anorexia, vomiting and constipation.

In statistical analyses of 10 pre-specified safety events, the incidence of rash/acne, diarrhoea and CTC grade 3 or 4 liver transaminases was significantly higher with gefitinib than carboplatin / paclitaxel ($p< 0.0001$). The incidence of neurotoxicity, nausea, vomiting and CTC grade 3 or 4 haematological toxicity (neutropenia, leukopenia, anaemia and thrombocytopenia) was significantly higher with carboplatin / paclitaxel than gefitinib ($p\leq0.0001$).

Overall, the incidence of ILD-type events was low but was higher in the gefitinib arm compared with the carboplatin / paclitaxel arm (2.6% and 1.4%, respectively). These events led to death in three gefitinib-treated patients and one carboplatin / paclitaxel-treated patient.

Post-hoc summaries of safety data by EGFR mutation status were produced. Median overall exposure to first-line gefitinib was 8.3 months in EGFR mutation positive patients, 5.9 months in EGFR mutation unknown patients and 1.6 months in EGFR mutation negative patients. Median overall exposure to first-line carboplatin / paclitaxel was 4.1 months in all EGFR mutation subgroups.

The safety profiles of the subgroups of patients with positive, negative, or unknown EGFR mutation status were consistent with the overall population and the known safety profile of gefitinib with regards to the type of AEs reported. Whilst there were some differences in the safety profile for gefitinib according to mutation status, which might be explained by differences in length of exposure, the relative safety profile for gefitinib compared with carboplatin / paclitaxel was favourable in each subgroup described by mutation status.

There were no new safety signals identified from these data.